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10/813,502	03/30/2004	Nicholas C. Nicolaides	MOR-0277	5311

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EXAMINER	
POPA, ILEANA	
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1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/813,502	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70 and 72-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70 and 72-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03/30/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. However, upon further consideration new grounds of rejection are made, as shown below.

2. Claims 1-69 and 71 have been cancelled.

Claims 70 and 72-77 are pending and under examination.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 70 and 73-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising the mutation in the preselected immunogen, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76).

The patent claims are drawn to: **(i)** a method of generating a mutation in a gene of interest (i.e., a preselected immunogen) by growing a population of mammalian cells expressing the gene of interest and a dominant negative allele of aPMS2 gene, wherein the dominant negative allele is a truncated human PMS2 (i.e., *in vitro* introduction, into the cell expressing a preselected immunogen, of a dominant negative allele of a PMS2

gene) and identifying a cell in which the preseleced immunogen is mutated (i.e., selecting the cell), wherein the cell is hypermutable (i.e., a method of generating a hypermutated preselected immunogen) (claims 11 and 16-18). Identifying/selection is by analyzing the sequence of the gene of interest or of the mRNA transcribed from the gene of interest (claims 12 and 13), i.e., determining whether the polynucleotide comprises a mutation as compared to the wild type, and **(ii)** a homogenous composition of cultured hypermutable, mammalian cells comprising a dominant negative allele of PMS2 (claim 7), wherein the dominant negative allele of PMS2 is human PMS2 (claim 8) comprising the first 133 amino acids of the human PMS2 (claims 9 and 10). The specification defines that the dominant negative allele of the human PMS2 is hPMS2-134 comprising codons 1-134 of the wild type hPMS2 (column 3, lines 27-32, Example 1), and therefore it is the same as the claimed truncated human PMS2 mutant, i.e., it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. It is noted that, since the claimed hPMS2-134 consists of codons 1-134 of the wild type hPMS2 it comprises the first 133 amino acids of the wild type hPMS2. With respect to the limitation of the cell being genetically stable, the mammalian cell of the patent is genetically stable enough once it acquires the mutation in the preselected gene since it is possible to detect this mutation. In alternative, it would have been obvious to one of skill in the art, at the time the invention was made, to restore the genetic stability of the mammalian cell once the desired mutation was obtained, by suppressing the activity of the dominant negative PMS2, with a reasonable expectation of success. One of skill in the art would have been motivated

to do so in order to obtain continuous expression of preselected genes comprising the desired mutations. Thus, the patented claims 7-13 and 16-18 anticipate claims 70 and 73-77 of the instant application. Since the claims of the U. S. Patent No. 6,146,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

4. Claims 70 and 72-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7, and 12 of U.S. Patent No. 6,808,894. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising the mutation in the preselected immunogen, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the

dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims recite: **(i)** a method for making a hypermutable antibody-producing cell *in vitro* by co-introducing into a cell an immunoglobulin gene (i.e., a preselected therapeutic immunogen) and dominant negative human PMS2 (claims 1, 3, and 6). The dominant negative human PMS2 has a truncation mutation at codon 134 (claim 4), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 5) and the method further comprises restoring genetic stability to the hypermutable cell (claim 12). Thus, the patent claims are drawn to a method of making a genetically stable cell expressing a hypermutated immunogen, i.e., expressing a polynucleotide encoding the preselected immunogen into a genetically stable cell, and **(ii)** a homogenous culture of isolated hypermutable mammalian cells wherein the cell produce antibodies and express a dominant negative truncated PMS2 mutant (claim 7). The specification discloses that DNA mutagens can be used to enhance the mutation rate (column 8, lines 1-10). With respect to the limitation of selecting cell comprising a mutation in the gene encoding the preselected immunogen based on analyzing the gene for the presence of said mutation as compared to the wild type, this is not innovative over the prior art. It would have been obvious to one of skill in the art to do so and one of skill in the art would have expected a reasonable expectation of success in doing such. One of skill in the art would have been motivated to do so in order to selected for cells expressing the desired mutations, for example mutations resulting in immunoglobulins with higher affinity for the antigen as compared to the wild type

immunoglobulins. Thus, the patented claims 1, 3-7, and 12 anticipate claims 70 and 72-77 of the instant application. Since the claims of the U. S. Patent No. 6,808,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

5. Claims 70 and 72-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6 of U.S. Patent No. 6,825,038. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising the mutation in the preselected immunogen, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims recite an *in vitro* method for generating a mutation in a gene of interest in a hypermutable cell (i.e., generating a hypermutated immunogen) by introducing into the hypermutable cell expressing the gene of interest a dominant negative PMS2 allele under the control of an inducible promoter, testing the cell for a mutation in the gene of interest, and stabilizing the genome of the cell expressing the mutated gene of interest by decreasing the activity of the dominant negative allele (claims 1 and 6), i.e., selecting cells comprising a mutation in the gene of interest. Testing comprises analyzing the nucleotide sequence of the gene of interest (claim 2) or the mRNA transcribed from the gene of interest (claim 3). With respect to the limitation of compare these sequences to the wild type, this is a requirement for the testing method. The specification discloses that DNA mutagens can be used to enhance the mutation rate (column 2, lines 61-65) and that the dominant negative PMS2 allele is hPMS2-134 (column 5, lines 1-67, Examples 1 and 2), i.e., it is the same as the claimed truncated human PMS2 mutant and therefore, it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. With respect to the limitation recited by the instant claim 77, one of skill in the art would have been motivated to obtain a homogenous population of cells expressing a mutated gene of interest in order to constantly produce this gene. Although the application claims do not recite controlling hPMS2-134 expression by an inducible promoter, one of skill in the art would have been motivated to modify the claimed invention and use such because inactivating hPMS2-134 would be easily achieved when needed, without additional manipulations. Thus, the patented claims 1-3 and 6 anticipate claims 70 and

72-77 of the instant application. Since the claims of the U. S. Patent No. 6,825,038 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

6. In addition of the above, Applicant is required to disclose any additional applications or patents that would be material for the patentability of this application.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

8. Claim 70 (72-77) is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim as written does not disclose the presence of a link between selecting a cell comprising a mutation in a preselected immunogen and expressing a polynucleotide encoding for the preselected immunogen in a genetically stable cell. Since it is unclear how these steps relate to each other, the metes and bounds of the claim cannot be determined and the claim is indefinite.

In alternative, claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps leading from selecting cells comprising a mutated preselected immunogen to expressing a

polynucleotide sequence encoding the mutated preselected immunogen in a genetically stable cell.

Claims 72-77 are rejected for being dependent from the rejected claim 70.

72-77

9. Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear from the language of the claim whether the genetically stable cell is the cell comprising the truncated dominant negative PMS2, the cell wherein the truncated dominant negative PMS2 was inactivated, or whether the polynuclotide encoding the mutated preselected immunogen is cloned and expressed in a different cell. Since the metes and bounds of the claim cannot be determined, the claim is indefinite.

Claims 72-77 are rejected for being dependent from the rejected claim 70.

Claim Rejections - 35 USC § 112, written description

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 70 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

The instant claims are drawn to a truncated mutant of a PMS2 (claim 70) or to a truncated human PMS2 (claim 73). Therefore, the claims encompass an enormous and variable genus of truncated PMS2 mutants from any source (claim 70), or a wide and variable genus comprising any truncated human PMS2 mutants (claim 73), the structure of which is not sufficiently disclosed in the specification and the claims.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude the inventors had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all its limitations using such

descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that the Applicants were in possession of the claimed invention (January 5, 2001, Fed. Reg., Vol. 66, No. 4, pp.1099-11).

In analyzing whether the written description requirement is met for the genus claims, it is determined whether representative numbers of species have been described by their complete structure and functional characteristics.

When the claims are analyzed in light of the specification, the truncated mutant can be any truncated PMS2 from any organism (claim 70) or any truncated human PMS2 (claim 73), as long as it is dominant negative. The genus of truncated mutants is very large; and a great deal of variability is encompassed by the instant claims. The instant claims encompass in their breadth any truncated PMS2 from any source (claim 70) or any truncated human PMS2 (claim 73); the truncated PMS2 is not particularly limited by its structure. The genus (i.e., the truncated PMS2) is described by its function to be dominant negative, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. The specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different truncated PMS2 variants. Applicant has not provided any information besides the characterization of the genus as having dominant negative activity. This limited

characterization, however, does not indicate that the Applicant had possession of the claimed genus of dominant negative truncations. Applicant is relying upon the dominant negative activity and the disclosure of one truncated variant, i.e., the human PMS2 comprising a mutation at codon 314, to support an entire genus. It is well known that minor structural differences among even structurally related compounds can result in substantially different biology. The specification fails to disclose what requirements a truncated variant must meet to have a dominant negative activity, i.e., the specification fails to provide the relationship between structure and function for these truncated variants. The specification does not contain any disclosure of the structure of all truncated variants. Therefore, Applicant has not disclosed the requisite structural features of the truncated PMS2 variants that would result in dominant negative activity, a feature deemed essential for the instant invention. One of skill in the art would not be able to predict that any truncation would result in a dominant negative activity. Therefore, one of skill in the art would not recognize Applicant to be in possession of the entire genus of biologically relevant peptides.

In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicant invented what was claimed. Consequently, the Applicant was not in possession of the instant claimed invention, at the time the application was filed.

Claims 72, 76, and 77 are rejected for being dependent from the rejected claim 70.

** It is noted that claims 74 and 75 are directly or indirectly dependent from claim

70.

Claim Rejections - 35 USC § 112, enablement

12. Claims 70, 72, 73, 76, and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a genetically stable cell expressing a hypermutated immunogen by introducing into the cell the dominant negative human PMS2, wherein the dominant negative human PMS2 comprises a truncation mutation at codon 134 (i.e., hPMS2-134), does not reasonably provide enablement for a method of making the said cell by using a truncation mutant of a PMS2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The claimed invention is drawn to a method of making a hypermutated immunogen. Such invention has use in the art for obtaining better immunogens for the generation of effective vaccines.

The instant claims are drawn to a cell comprising any truncation mutant of any PMS2 (claims 70, 72, 76, and 77) or any truncation mutant of the human PMS2 (claim 73). The aspect considered broad is the range of dominant negative truncated mutants that can be used to obtain the genetically stable cell that produces the hypermutated immunogen. As will be shown below, this broad aspect is not enabled for its embraced full scope.

The specification as filed teaches hPMS2-134, which is a dominant negative truncated human PMS2. Beside this hPMS2-134, the specification as filed fails to disclose any other transdominant truncation mutant of the human or any other PMS2.

The state of the art of mismatch repair (MMR) genes teaches that during the process of gene repair, MMR genes form heterodimeric combinations and that the interaction between various MMR genes is complex and still a matter of debate and ongoing research. For example, Jiricny (Nature Genetics, 2000, 24: 6-8) teaches that in human cells, MMR is a complex process mediated by MSH2, MSH3, MSH6, MLH1, and PMS2. Mismatch recognition in human cells is carried out mainly by the heterodimeric combination of MSH2 and 6; this complex acts in the repair of mismatches and of insertions and deletions loops (IDLs) arising during DNA replication. A second, less abundant, heterodimeric complex composed of MSH2 and 3 can mediate the repair of IDLs in the absence of MSH6. The loss of MSH2 therefore, leads to accumulations of

point and frame shift mutations resulting from unpaired IDLs, detectable as high microsatelite instability (MSI-H). Due to the redundant function of MSH3 and 6 in IDL repair, cells lacking the former have no apparent phenotype, whereas cells lacking the latter accumulate predominantly point mutations (p. 6, column 2). Jiricny teaches that, as with MSH2 in mismatch recognition, MHL1 is a key player in MMR. Interaction between MLH1 and PMS1/MLH3 have been reported, but only the MLH1/PMS2 heterodimer has been shown to participate in MMR (p. 6, column 3) and that cells lacking PMS2 retain residual IDL repair activity with MLH3 being the most likely candidate for this residual activity (p. 7, column 1).

Considering the complex mechanism of MMR, the main issue in the instant case is whether any truncated PMS2 would function as a dominant negative mutant and what truncation in any PMS2 and what truncations in the human PMS2 gene would result in a dominant negative activity. It is noted that, while other PMS2 mutants are known, their dominant activity is not described either in the art or the specification, and the art of obtaining such mutants is unpredictable. The specification fails to provide any evidence that truncated PMS2 mutants, other than hPMS2-134, have dominant negative activity. The specification does not provide any guidance as to what other truncations would result in the production of PMS2 dominant negative mutant able to inhibit MMR in the cells that would express such a mutant. It is noted that not any truncated PMS2 mutant would function in a dominant negative manner, and the specification does not provide working examples or guidance as to what specific truncations are required to change the wild type PMS2 to a dominant negative protein. Making dominant negative mutants

of any MMR gene, including PMS2, is not routine in the art and, without sufficient guidance to a specific truncation, one of skill in the art would require undue experimentation to find a truncated mutant, as claimed. It is noted that the unpredictability of obtaining such truncated mutants alone provides reasonable doubt as to whether the broad instant claims are enabled.

In conclusion, the specification is enabling only for a method of making a genetically stable cell expressing a hypermutated immunogen by introducing into the cell the dominant negative human PMS2, wherein the dominant negative human PMS2 comprises a truncation mutation at codon 134.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 70, 73-75, and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641).

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2.

Nicolaides et al. teach a truncated human PMS2 mutant that has a truncation mutation at codon 134 (hPMS2-134) that has a dominant negative activity and confers a dominant negative MMR defect when transfected into cells (claims 70, 73, and 74) (p. 1635, column 1, p. 1640, column 1). It is noted that the hPMS-134 of Nicolaides et al. is the same as the one recited in the instant claims and therefore, it must comprise thymidine at nucleotide 424 as the truncation mutation (claim 75). Nicolaides et al. also teach a method of producing a hypermutated β-galactosidase (i.e., hypermutated preselected immunogen) by introducing the hPMS2-134 into hamster fibroblasts comprising the pCAR-OF reporter construct having the β-galactosidase gene with a 58-bp out-of-frame poly(C-A) tract at its 5' end, wherein the pCAR-OF does not generate β-galactosidase unless a frame restoration mutation (i.e., insertion or deletion) arise following transfection with hPMS2-134 (p. 1636, column 2 bridging p. 1637). Nicolaides et al. teach that introduction of hPMS2-134 into the hamster fibroblasts disturbs their MMR activity with a resulting higher frequency of mutations within the pCAR-OF reporter and restoration of the β-galactosidase open reading frame (p. 1637, columns 1 and 2, p. 1638, column 1). They also teach cloning cells comprising the gene encoding for the mutated β-galactosidase, i.e., they teach selection for cells expressing the mutated β-galactosidase and a homogenous culture of these cells (claims 70 and 77) (p. 1637, column 2, p. 1638, column 1, Fig. 4). With respect to the limitation of the cell being genetically stable, the cell of Nicolaides et al. is genetically stable enough once it acquires the mutation in the β-galactosidase gene since the protein can be easily detected and therefore, the gene encoding for the mutated β-galactosidase is

expressed in a genetically stable cell. Since Nicolaides et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

15. Claims 70 and 73-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Nicolaides et al. (U.S. Patent No. 6,146,894).

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Nicolaides et al. teach a method of generating a mutation in a gene of interest (i.e., a preselected immunogen) by growing a population of mammalian cells expressing the gene of interest and a dominant negative allele of aPMS2 gene, wherein the dominant negative allele is a truncated human PMS2 (i.e., *in vitro* introduction, into the cell expressing a preselected immunogen, of a dominant negative allele of a PMS2 gene) and identifying a cell in which the preseleced immunogen is mutated (i.e., selecting the cell), wherein the cell is hypermutable (i.e., a method of generating a hypermutated preselected immunogen) (claims 70 and 76) (column 3, lines 50-67, column 4, lines 43-61, column 5 bridging column 6, claims 1 and 3).

Identifying/selection is by analyzing the sequence of the gene of interest or of the mRNA transcribed from the gene of interest (column 6, lies 8-12, claims 12 and 13). With respect to the limitation of determining whether the polynucleotide comprises a mutation as compared to the wild type (claim 76), this is a requirement of the method, since in the absence of a comparison there would be no identification of any mutation. Nicolaides et al. also teach a homogenous composition of cultured hypermutable, mammalian cells obtained by the method above (claim 77) (column 5 bridging column 6, claim 7). The dominant negative allele of PMS2 is hPMS2-134 (claims 73-75) (column 3, lines 27-32, column 4, lines 8-22, Example 1), and therefore it is the same as the claimed truncated human PMS2 mutant, i.e., it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. With respect to the limitation of the cell being genetically stable, the mammalian cell of the patent is genetically stable enough once it acquires the mutation in the preselected gene since it is possible to detect this mutation. Since Nicolaides et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 70 and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641), as applied to claims 70, 73-75, and 77 above, in view of Nicolaides et al. (U.S. Patent 6,825,038).

** The instant rejection is based on the interpretation that the genetically stable cell is either the cell comprising hPMS2-134, or the cell expressing hPMS2-134 wherein the hPMS2-134 is inactivated.

Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641) do not teach at least one DNA mutagen (claim 72) or analyzing the polynycleotide encoding the mutated preselected immunogen (claim 76). In their U.S. Patent 6,825,038, Nicolaides et al. teach exposing the cells comprising hPMS2 to DNA alkylating agents or other DNA mutagens and analyzing the polynycleotide encoding the preselected immunogen for the presence of mutations (column 2, lines 61-65, column 3, lines 30-34, Example 3, claims 2 and 3). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641) by using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Nicolaides et al. (U.S. Patent 6,825,038), who teach a higher rate of hypermutation in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of DNA alkylating agents for mutations accumulation. The limitation of determining the mutations in the β-galactosidase by analyzing this gene is not innovative over the prior art, since doing such is routine in the art (see also Nicolaides et al., U.S. Patent 6,825,038, column 7, lines 45-54). With

respect to the limitation of the cell being genetically stable, the cell of Nicolaides et al. is genetically stable enough once it acquires the mutation in the β-galactosidase gene since the protein can be easily detected and therefore, the gene encoding for the mutated β-galactosidase is expressed in a genetically stable cell. In alternative, it would have been obvious to one of skill in the art, at the time the invention was made, to restore the genetic stability of the mammalian cell once the desired mutation was obtained, by suppressing the activity of the dominant negative PMS2, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain continuous expression of preselected genes comprising the desired mutations. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that this could be accomplish by routine experimentation (see Nicolaides et al., U.S. Patent 6,825,038, column 3, lines 30-65, Example 4). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

18. Claims 70 and 73-77 are rejected under 35 U.S.C. 102(e) as being unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894), as applied to claims 70 and 73-77 above, in view of Nicolaides et al. (U.S. Patent 6,825,038).

The applied reference has a common invetnor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al. (U.S. Patent No. 6,146,894) do not teach at least one DNA mutagen (claim 72). In their U.S. Patent 6,825,038, Nicolaides et al. teach exposing the cells comprising hPMS2 to DNA alkylating agents or other DNA mutagens (column 2, lines 61-65, column 3, lines 30-34, Example 3). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641) by using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Nicolaides et al. (U.S. Patent 6,825,038), who teach a higher rate of hypermutation in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of DNA alkylating agents for mutations accumulation. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

19. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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